biological siblings living in the same household and in those adopted out of the family. This study estimated a heritability of 41% for anxiety disorders in families affected by bipolar disorder. Similarly, psychological factors in the origins of anxiety comorbid with bipolar disorder have been substantially understudied, although recent reports suggest that personality traits such as perfectionism might have an important mediating role.[9]

Finally, research into the development of effective treatments for patients with this comorbidity has been surprisingly scarce. Most clinical therapeutic guidelines, whether psychological or pharmacological, extrapolate recommended treatments from those developed for patients with primary anxiety disorders. Few studies of novel treatments for comorbid anxiety in bipolar disorder have been reported, with those undertaken suggesting some very limited benefit of psychological treatments such as cognitive behavioural therapy,[10] or medications such as quetiapine, an antipsychotic.[11] However, no treatments have been shown to be of major effect.

In conclusion, Pavlova and colleagues' meta-analysis[1] confirms the high prevalence of anxiety disorders comorbid with bipolar disorder. This finding, in conjunction with growing evidence for increased morbidity and mortality for those with this co-occurrence, draws attention to the dearth of research into causative processes and the development of new treatments. By focusing on these issues, Pavlova and colleagues provide a much needed and urgent wake-up call for this field.

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1 Pavlova B, Alda M, Uher R. Lifetime prevalence rates in anxiety disorders in people with bipolar disorder: a meta-analysis. *Lancet Psychiatry* 2015; published online June 24. http://dx.doi.org/10.1016/S2215-0366(15)00112-1.
2 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th edn. Arlington: American Psychiatric Publishing, 2013.
3 Goes FS. The importance of anxiety states in bipolar disorder. *Curr Psychiatry Rep* 2015; **17:** 3.
4 Vazquez GH, Baldessarini RJ, Tondo L. Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview. *Depress Anxiety* 2014; **31:** 196–206.
5 Mitchell PB, Johnston AK, Frankland A, et al. Bipolar disorder in a national survey using the World Mental Health Version of the Composite International Diagnostic Interview: the impact of differing diagnostic algorithms. *Acta Psychiatr Scand* 2013; **127:** 381–93.
6 Perich T, Lau P, Hadzi-Pavlovic D, et al. What clinical features precede the onset of bipolar disorder? *J Psychiatr Res* 2015; **62:** 71–77.
7 Nurnberger JI Jr, McInnis M, Reich W, et al. A high-risk study of bipolar disorder. Childhood clinical phenotypes as precursors of major mood disorders. *Arch Gen Psychiatry* 2011; **68:** 1012–20.
8 Song J, Bergen SE, Kuja-Halkola R, et al. Bipolar disorder and its relation to major psychiatric disorders: a family-based study in the Swedish population. *Bipolar Disord* 2015; 17: 184–93.
9 Corry J, Green M, Roberts G, et al. Anxiety, stress and perfectionism in bipolar disorder. *J Affect Disord* 2013; **151:** 1016–24.
10 Stratford HJ, Cooper MJ, Di Simplicio M, et al. Psychological therapy for anxiety in bipolar spectrum disorders: a systematic review. *Clin Psychol Rev* 2015; **35:** 19–34.
11 Sheehan DV, Harnett-Sheehan K, Hidalgo RB, et al. Randomized, placebo-controlled trial of quetiapine XR and divalproex ER monotherapies in the treatment of the anxious bipolar patient. *J Affect Disord* 2013; **145:** 83–94.

Does cigarette smoking cause psychosis?

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See Articles page 718

Many psychiatrists note that their patients, particularly those with schizophrenia, smoke cigarettes—and usually smoke heavily. This association has typically been assumed to be some form of self-medication, but in *The Lancet Psychiatry*, a systematic review by Pedro Gurillo and colleagues[1] brings together evidence showing that cigarette smoking might actually be a cause of psychosis.

In case-control studies, an overall increase was noted in the odds of first-episode psychosis in cigarette smokers versus non-smokers (odds ratio 3·22, 95% CI 1·63–6·33), albeit with some evidence of publication bias. Daily smokers also developed psychotic illness about 1 year earlier than did non-smokers. In prospective studies, of which only five were identified by the systematic review, the relative risk of new psychotic disorders in daily smokers versus non-smokers was 2·18 (95% CI 1·23–3·85). This difference in apparent risk by study design suggests recall bias in the case-control estimate, but the self-medication hypothesis is not mutually exclusive with the possibility that smoking is a causal risk factor for psychosis.

The most likely explanation of these findings is that cigarette smoking is associated with an increased risk for schizophrenia. Taking up, and continuing, smoking could be self-medication for anxiety, depression, or psychotic symptoms. It could also be shared with other risk factors for psychosis, such as family history, urban upbringing, or childhood adversity. Each of these risk

factors, in addition to early and regular cannabis use, seems to have an additive effect in terms of phenotypes such as psychosis and age at onset.[2–4]

Primacy, the strength of an association, dose response, and specificity are among the best indicators of causality in an association. Little doubt exists that cigarette smoking usually precedes psychosis, but prospective studies are scant and few of those published have carefully addressed possible confounders. Few readers will view a relative risk of 2·18 to be convincing. Smoking is also unlikely to be judged a specific cause of psychosis. Moreover, the age-at-onset data do not really help to establish causality, because smoking could advance age at onset without necessarily causing psychosis.

One intriguing possible interpretation of these findings is that the genes for psychosis overlap with those for cigarette smoking. Indeed, they probably do. The Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) described 108 separate genetic loci associated with an increased risk of schizophrenia.[5] One of these is located in a cluster of genes—*CHRNA5*, *CHRNA3*, and *CHRNB5*—on chromosome 15, and this region is associated with both early age at onset of smoking and heavy smoking.[6,7] The PGC might have data available, or could possibly gather it, to test the possibility that this genetic proxy for heavy smoking is associated with schizophrenia in smokers but not in non-smokers and, thus, provide evidence that smoking is on the causal pathway to schizophrenia.

If cigarette smoking is causal, one has to ask why the typical age of taking up regular daily smoking is during the teenage years, but the usual age at onset of psychosis is around 25 years. Regular smoking is unlikely to take years to exert a psychotogenic effect but, then again, most smoking-related diseases only arise after prolonged exposure. Perhaps smoking cigarettes acts as a so-called gateway drug to cannabis and other psychotomimetics; conversely, the association of cannabis with psychosis could be attributable to the tobacco with which most cannabis is consumed. Thus far, no studies have investigated the age at onset of psychotic illness while measuring both cannabis and cigarette smoking. In a previous meta-analysis, a pooled interval of 5·3 years was estimated between age at initiation of daily tobacco use and onset of psychosis.[8] It is noteworthy in that study that the difference in age at onset of psychosis in cannabis users was 2·7 years, compared with 1·0 years for cigarette smokers.[1] What is also apparent from published work is that co-use of both cigarettes and cannabis is common in young people and is associated with a worsening of mental health symptoms.[9] Kandel and Kandel[10] have summarised an impressive amount of in vitro and in vivo work, in keeping with the view that tobacco is a gateway drug to other substances of misuse, but epidemiological evidence is, as yet, absent.

Large, longitudinal, prospective studies are needed to investigate the relations between smoking tobacco and cannabis and development of anxiety, depression, and psychotic disorders, adjusting for the effects of other substances, to enable more stringent examination of whether cigarette smoking has a causal role in the development of psychosis. Such studies will allow us to assess the public health importance of the results presented here. To say that smoking causes psychosis would be premature, but the time might not be too much longer before cigarette smoking is recognised as a risk factor for psychosis as well as anxiety and depression.

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1 Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. *Lancet Psychiatry* 2015; published online July 10. http://dx.doi.org/S2215-0366(15)00152-2.
2 Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch Gen Psychiatry* 2011; **68:** 555–61.
3 Esterberg ML, Trotman HD, Holtzman C, Compton MT, Walker EF. The impact of a family history of psychosis on age-at-onset and positive and negative symptoms of schizophrenia: a meta-analysis. *Schizophr Res* 2010; **120:** 121–30.
4 Stepniak B, Papiol S, Hammer C, et al. Accumulated environmental risk determining age at schizophrenia onset: a deep phenotyping-based study. *Lancet Psychiatry* 2014; **1:** 444–53.
5 Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511:** 421–27.
6 Hartz SM, Short SE, Saccone NL, et al. Increased genetic vulnerability to smoking at *CHRNA5* in early-onset smokers. *Arch Gen Psychiatry* 2012; **69:** 854–60.
7 Gage SH, Munafò MR. Rethinking the association between smoking and schizophrenia. *Lancet Psychiatry* 2015; **2:** 118–19.
8 Myles N, Newall HD, Curtis J, Nielssen O, Shiers D, Large M. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. *J Clin Psychiatry* 2012; **73:** 468–75.
9 Ramo DE, Liu H, Prochaska JJ. Tobacco and marijuana use among adolescents and young adults: a systematic review of their co-use. *Clin Psychol Rev* 2012; **32:** 105–21.
10 Kandel ER, Kandel DB. Shattuck lecture: a molecular basis for nicotine as a gateway drug. *N Engl J Med* 2014; **371:** 932–43.